Status of Claims

Claims 24-28 are pending in the application. Claims 24 and 27 have been objected to. Claims 24-28 have been rejected. Claims 24 and 27 have been amended. Support for the amendment of claim 24 to an "exogenously supplied osteoinductive matrix" can be found throughout the Specification, see for example, Examples 1, 3, 8, 9, 11, 14 and 15. Further amendment of claim 24 and amendment of claim 27 are of an editorial nature and no new material has been added. Support for new claim 29 can be found throughout the Specification, see for example, Example 1.

Claim Objections

In the Office Action, the Examiner objected to claims 24 and 27 because of alleged informalities, namely, the recitation of "bone morphogenetic protein" and of "bone morphogenesis protein". Claims 24 and 27 have been amended to recite "bone morphogenic protein" in order to cure these informalities. Accordingly, Applicants request withdrawal of the objection.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

Claims 24-28 were rejected by the Examiner rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants note that the Examiner refers to the rejection of claims 1, 2, 8-9, 11 and 14-19 under 35 U.S.C. § 112, first paragraph. Pending claims 1-23 were cancelled and new claims 24-28 were added in a Supplemental Amendment filed March 29, 2004. Thus, the rejection is improper and Applicants accordingly request withdrawal of the rejection.

The Examiner alleged lack of support for implanting mesenchymal stem cells (MSC) "in the absence of an exogenously supplied matrix". Applicants disagree. In Example 2 of the published Application (US 2002/0102728) Applicants demonstrated transplantation of BMP-2-expressing C.9 cells into a segmental defect, in the absence of an exogenously supplied

matrix, and localization of the cells in the gap after one week (page 4, paragraph 30). Further, the transfected mesenchymal stem cells of the present invention were useful in building bone when administered with no matrix at all, only a collagen gel (see Example 14, pages 16-17, paragraph 202). Thus, Applicants have provided written description for the instant claims in the form of exemplification and accordingly, Applicants request withdrawal of the rejection.

Claims 24-28 were rejected by the Examiner rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants disagree.

The Examiner alleged lack of enablement for a method of inducing organized, functional bone formation by implanting genetically engineered mesenchymal stem cells (MSCs) in the absence of an exogenously supplied matrix, stating that bone formation "cannot occur by simply implanting MSCs in the absence of a support matrix". The Examiner further alleged that the art at the time of filing of the subject application describes the necessity of a support matrix for retaining cells and cell factors for organized, functional bone formation. Applicants disagree. Applicants submit, as described *supra*, that BMP-2-expressing C.9 cells localize in a segmental defect, in the absence of any exogenously supplied matrix. Further, claim 24 has been amended and recites "implanting said cultured mesenchymal stem cell in the absence of an exogenously supplied osteoinductive matrix at a site of bone infirmity". Examples 1, 2, 3, 8, 9, 11, 14 and 15 provide exemplification of transplantation *in vivo* of cultured mesenchymal stem cells transformed with BMP-2 and mounted on collagen sponges, or collagen gels containing BMP-2-transformed MSCs. Applicants demonstrated in Example 8 that regulated expression of BMP-2 was highly effective in promoting bone formation at a segmental defect site, in the absence of an exogenously supplied osteoinductive matrix. Applicants maintain that the collagen sponge used in the above-mentioned Examples is not osteoinductive. Figure 6B of Moutsatsos *et al.*, Molecular Therapy 3:449-461, 2001 shows that no bone was formed when a collagen sponge was implanted with unactivated C9 cells (BMP2 gene shut off). Further, in Figure 4i of the same reference no bone formation is seen in an ectopic transplantation site. Applicants submit that Applicants have shown that MSC-BMP-2 appropriately home to the site of injury, align

along defect edges, and are incorporated in newly formed bone trabecules, forming quantitatively and qualitatively superior bone. Thus, Applicants have provided sufficient description in the specification and support in the form of exemplification to enable one skilled in the art to make and use the claimed invention and accordingly, Applicants request withdrawal of the rejection.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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